GlaxoWellcome

March 25, 1999

1349 '99 MAR 26 A10:31

Management Dockets
Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number: 98D-0994

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry - BACPAC I: Intermediates in Drug Substance Synthesis, Chemistry, Manufacturing and Controls Documentation.

Please feel free to call me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,

Suva B. Roy.

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98D-0994

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Comments from GlaxoWellcome on the Draft Guidance for Industry
BACPAC I: Intermediates in Drug Substance Synthesis
Chemistry Manufacturing and Controls Documentation

General Comments

The pragmatic thinking in limiting the scope of this draft guidance recognizes the fact that early modifications up to the final intermediate are generally less likely to have an adverse impact on the drug substance and the drug product is commendable. We also commend the Agency that the guidance strives to provide for less burdensome notice of certain post approval changes within the meaning of 21CFR 314.70(a).

However, the draft guidance contradicts these premises by applying requirements that are appropriate for the actual drug substance to these intermediates, and also requiring the level of documentation, submission, approval and GMP requirements beyond current practice. For example, the guidance is:

1) Inappropriately extending 0.1% limit for new impurity (the ICHQ3A standard) to these early intermediates, especially since these intermediates will under go further processing and purification;
2) Inappropriately extending the ICHQ3C Option 1 for residual solvents to these intermediates, since they will under go further processing and purification where any residual solvent will be either eliminated or further reduced; and
3) Extending the GMP compliance and inspection standards for the drug substance to the manufacturing sites of the intermediates. The FDA's Guide to Inspection of Bulk Pharmaceutical Chemicals, September 1991 states on page 4, "Although strict observance of GMPs, approaching or equaling those expected for finished drug products, may be expected in some types of bulk processes, in most others it is neither feasible nor required to apply rigid controls during early processing steps. In all processes of this type, however, the requirements should be increasingly tightened according to some reasonable rationale." The Draft Guidance for Industry Manufacturing, Processing, or Holding of Active Pharmaceutical Ingredients, March 1998 states on page 16, "Less stringent in-process controls may be appropriate in early processing steps whereas tighter controls should be applied to later synthesis, isolation, and purification steps." Currently, as a matter of practice the FDA's compliance only inspects the site for final drug substance synthesis and not the individual sites where intermediates are made, unless specifically requested by the reviewer.

In order to be most beneficial, this guidance should focus only on establishing equivalence of the impurity profile of intermediates. The guidance itself recognizes this when it states, "Equivalence of the impurity profile may be established by testing any isolated intermediate following the change, including the final intermediate, or the drug substance." The guidance can be simplified by:

1) Deleting all references to site, GMP inspection status of intermediate manufacturing facilities, equipment and process changes;
2) Retaining only data requirements to establish equivalence whenever there is a significant change;
3) Requiring all such data be filed in Annual Reports; and
4) Deleting the three subsections for specification changes, and reporting specification changes in Annual Reports. These will significantly reduce regulatory burden without compromising safety and quality of the drug substance.

Specific Comments

120-121 - We suggest replacing the sentence, "When new methods are developed for this purpose, validation data should be provided" with, "When new methods are developed they should be appropriately validated for the purpose."

We also recommend that similar statements throughout the draft guidance be changed to reflect that the methods should be appropriately validated for the purpose. While the need for detailed validations of methods may be justified for later stages of synthesis to be covered in BACPAC-II, full validations for methods for early intermediates and in-process tests are disproportionate in BACPAC-I.

123-124 - The requirement that data from three post modification batches be compared to the historical data from ten premodification commercial batches is rather proscriptive. Small volume products or orphan drugs may have problems meeting the numerical batch requirements. We recommend the following as an alternative, "The level of impurities should be assessed by comparing postmodification batches to the largest range of available historical data from premodification batches. In order that the comparison is meaningful, comparison from three postmodification batches and ten premodification batches are encouraged but are not essential. Upper statistical limits of historical data may be applied when appropriate."

132-136 - The requirement that no new impurity greater than 0.1% for early stage intermediates is unreasonable. Even the draft guidance acknowledges this on lines 134-136, "Further reduction of impurity levels will frequently occur in the subsequent steps or steps prior to drug substance formation." We recommend that lines 132-136 be deleted.

137-138 - We recommend replacing the sentence, "Existing impurities, including residual organic solvents, are at or below the upper statistical limit of historical data" with, "Existing impurities, including residual solvents, if relevant, are within the stated limits or if limits are not specified at or below the historical data. The upper statistical limit of the historical data may also be used when appropriate."

139-140 - We recommend replacing the sentence, "Total impurities are at or below the upper statistical limit of historical data" with, "Total impurities are within stated limits or, if limits are not specified, at or below the historical data. The upper statistical limit of the historical data may also be used when appropriate."

173-177 - This bullet is confusing. One should be able to repeat crystallization or a purification stage as/when needed to achieve equivalence to the pre-change final intermediate. Additional purification steps, such as charcoal treatment or recrystallization steps are routinely written into the process for the drug substance. It is important not to lose sight of the fact that the quality of the final intermediate that is carried forward is what is important, so if an additional purification step achieves the goal, it logically belongs under the BACPAC-I.

200 - We recommend replacing the sentence, "Conformance to historical particle size distribution profile" with, "Conformance to historical particle size distribution profile, where appropriate. The registered particle size measuring technique should be used to provide a one-to-one comparison of the post change material to the pre-change material."

205-325 - This section on Site, Scale, and Equipment Changes appears to have been modeled after the SUPACs. While requirements are reasonable for dosage forms, the same requirements for these intermediates are disproportionate and contradict the premise of this guidance that "early modifications up to the final intermediate are generally viewed as less likely to have an adverse impact on the drug substance and the drug product." The draft guidance itself recognizes this when it states, "Under these constraints, the changes in this category should not usually give rise to different impurity profiles for either the intermediates following the change or the drug substance." We recommend simplifying this section by deleting all references to site, GMP inspection status of intermediate manufacturing facilities, equipment and process changes, and retaining only data requirements to establish equivalence whenever there is a significant change. Such data to be filed in Annual Reports.

217-219 - We recommend "company-owned" be defined in the glossary. For example would a part ownership in a facility qualify it as company-owned? What proportion of a part ownership should a company own to call the site as "company owned"?

328 - We recommend that changes to the final intermediate specifications should be included under BACPAC-I. This is consistent with our comments on lines 173-177.

326 - Specification changes - this section appears to have been modeled after 21CFR314.70. As the guidance itself notes, changes in early intermediates are very unlikely to affect the specification of the drug product since the intermediates will under go subsequent processing. Also, the issue of specification changes affecting drug substance quality becomes moot as long as equivalence is shown at that step or a following step. We recommend that this section be simplified by deleting the three subsections and requiring changes in specifications of intermediates including final intermediate be reported in Annual Reports.

330 - Generally intermediates do not have compendial monographs. This section should be deleted. Also compendial methods are already validated and do not require revalidation so the proposed requirement is confusing.

354-398 - We recommend that the Changes Being Effected (CBE) filing requirement be changed to Annual Reports (AR). Also see comment for specification changes.

405-440 - We recommend that the CBE filing be changed to AR as long as equivalence is established at any intermediate step following the change or at the drug substance stage.

443-478 - We recommend that the both CBE and Prior-Approval Supplement (PAS) be changed to AR on the demonstration of equivalence at any intermediate step or at the drug substance stage. Non-equivalence at the drug substance stage will result in a change in specification and thus a PAS anyway.

485-532 - We recommend that the CBE filing be changed to AR as long as equivalence is established at any intermediate step following the change or at the drug substance stage. Non-equivalence at the drug substance stage will result in a change in specification and thus a PAS.

503-505 - This is a GMP issue and should not be included in the guidance. We recommend that this be deleted.

521-522 - We recommend deleting the sentence, "If the level of new solvent in an intermediate is at or below the ICHQ3C, Option 1, no testing of the drug substance is needed." The ICHQ3C provisions apply to the drug substance so it is inappropriate to extend it to the intermediates. Again, the intermediates will undergo further processing so as long as equivalence with respect to residual solvent is demonstrated at that step or a subsequent step the issue is moot.

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WOSL 0595
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